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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/678,202	09/29/2000	David Bar-Or	4172-3	3734

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 05/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/678,202	BAR-OR ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26,28-31 and 375-381* is/are pending in the application.

4a) Of the above claim(s) *12-20,25,26 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,8-11,21-24,28-30 and 375-381* is/are rejected.

7)☒ Claim(s) *2 and 5-7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the response filed 4/9/04, claims 1, 28, 29, 31 have been amended, claim 27 cancelled, and claims 375-381 added. Claims 1-26, 28-31 and 375-381 are pending.

Claims 12-20 remain withdrawn from consideration, since they do not encompass the elected specie. Claims 25-26 are also withdrawn. Among the elected species is a choice of diseases with which the animal is afflicted. The chosen disease is ischemia. Claim 25 recites "neurological trauma", and as such would encompass blunt trauma, e.g., a head injury; this is not the same as ischemia. Similarly, most neurodegenerative diseases are not caused by ischemia. Accordingly, the inventions of claims 25 and 26 are not strictly within the elected specie. In a similar vein, claim 31 is withdrawn, since "radiation therapy" would be more appropriately administered to a subject afflicted with cancer than ischemia.

Claims 1-11, 21-24, 28-30, 375-381 are examined in this Office action.

Applicants' arguments filed 4/9/04 have been considered and found persuasive. The previously imposed rejections are withdrawn.

As before, the abbreviation **ROS** hereinbelow refers to *reactive oxygen species.*

✧

The specification is objected to.

- On page 6, line 7, a "web" address is provided. The contents are transient, and as such, reference to this address should be eliminated from the disclosure. Applicants have argued that it is not necessary to delete this. However, applicants can provide no assurance that, in the year 2019 for example, the information supplied at that web address will be identical to what it was in 1999, or indeed that the web address will exist at all. The objection is maintained.

- As indicated previously, there is an error in Figs 1A - 1D. Double bonds are missing from the imidazole group. In response to this objection, applicants have submitted a new figure. However, the issue raised by the examiner has not been acknowledged by applicants, and the error that was previously present is still present.

✧

Claim 1 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of copending application Serial No. 10/186168. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claimed inventions are substantially the same. [This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented].

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In re Vogel, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application . See 37 CFR 1.78(d)

✧

Claims 21-24, 28-30, 375-381 are rejected under 35 U.S.C. §112 second paragraph, as

being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Each of claims 21-24, 28-30, 375-381 is dependent on a non-elected claim.

✧

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 1, 9, 10, 21-24, 28-30, 375-381 are rejected under 35 U.S.C. §103 as being unpatentable over Deghenghi (USP 5,932,548).

Deghenghi discloses (col 4, line 10) the following peptide:

Tyr-Ala-His-D-Mrp-Ala-Trp-D-Phe-Lys-NH_2

Also disclosed is that this is one of several peptides that is useful for treatment of myocardial ischemia. Accordingly, whatever damage is caused by ROS (or any other molecular

entities) in the manifestations of ischemia will be mitigated.

Thus, the claims are rendered obvious.

✧

Claims 1, 21-24, 28-30, 375-381 are rejected under 35 U.S.C. §103 as being unpatentable over Rosenzweig (WO 00/23469).

Rosenzweig discloses (page 26, line 21) a method of treating ischemic injury by administering any of several peptides. Among those are the peptides designated SEQ ID NO: 6, 15, 16, 29-34 and 37, all of which have a histidine at the requisite position.

Thus, the artisan of ordinary skill would reason that if the peptides are effective to treat ischemic injury, then it will necessarily be true that the "damage" which gave rise to the ischemic injury is mitigated as well.

Thus, the claims are rendered obvious.

✧

Claims 1, 3, 9, 21-24, 28-30 are rejected under 35 U.S.C. §103 as being unpatentable over Liotta (USP 5,270,447) in view of Malins (*Proc. Natl. Acad Sci.* **93**, 2557, 1996); or Liotta in view of Knight (*Ann Clin Lab Sci* **25**, 111, 1995).

Liotta discloses (figure 6; col 5, line 3; table I, cols 5-6) the following peptide:

AA**H**EEICTTNEGVM

Also disclosed (e.g., col 15, line 56+) is that the peptide can be used to treat cancer.

Liotta does not disclose that tumor cell growth is caused by reactive oxygen species. Malins and Knight both disclose that tumor cell growth is caused at least in part by reactive oxygen species. Neither of Malins and Knight discloses a peptide falling with the scope of instant claim 1.

One of ordinary skill would expect that if cancer is caused by ROS, or if tumor cells give rise to ROS (or if both is true), then eliminating (at least in part) the tumor cells can only take place if the damage caused by the ROS has been mitigated. It may be the case that Liotta does not teach that the disclosed peptides act to directly reduce the formation of ROS. However, given that tumor cells increase the level of ROS, it follows therefrom that if the population of tumor cells is reduced, the amount of ROS produced by the tumor cells will be reduced as well. If the amount of ROS that is produced declines, then it stands to reason that the "damage" caused by those ROS's will also decline.

Thus, the claims are rendered obvious.

✧

Claims 1, 3, 9, 10, 21-24, 28-30 are rejected under 35 U.S.C. §103 as being unpatentable over Blaschuk (USP 6,610,821) in view of Malins (*Proc. Natl. Acad Sci.* **93**, 2557, 1996); or Liotta in view of Knight (*Ann Clin Lab Sci* **25**, 111, 1995).

Blaschuk discloses various peptides falling within the scope of instant claim 1 including (col 4, line 11) SEQ ID NO: 36, which has the following sequence:

Cys-Ser-**His**-Ala-Val-Cys

It is also true that there is an acetyl group bonded to the N-terminus, and the two cysteine sulfhydryl groups are bonded together in disulfide linkage. Blaschuk also discloses that the compounds are effective to reduce tumor cell angiogenesis and to reduce tumor cell volume.

Blaschuk does not disclose that tumor cell growth is caused by reactive oxygen species. Malins and Knight both disclose that tumor cell growth is caused at least in part by reactive oxygen species. Neither of Malins and Knight discloses a peptide falling with the scope of instant claim 1.

The first issue concerns the structure of the peptide itself. Instant claim 1 specifies the "sequence" of the peptide which is to be used, but stops short of using the "consisting of" language. Claim 1 can be reasonably interpreted as encompassing any peptide as long as the "sequence" of that peptide falls within the scope of "P_1-P_2" (as these variables are defined). Claim 1 would therefor permit any substituent to be bonded to the *alpha*-amino group of Xaa_1, provided that the substituent is not itself an amino acid or peptide. If, for example, an acetyl group were bonded to the *alpha*-amino group of Xaa_1, the "sequence" (*per se*) of the peptide "P_1-P_2" would not be affected one way or another. [Claim 1 would also permit other modifications to any of "Xaa_4", but that issue will not be discussed at this point]. Similarly, the fact that two cysteines may be bonded together (in

disulfide linkage) does not affect the "sequence" of the peptide. Vast numbers of peptides and proteins have been tabulated over the years, a substantial portion of which contain disulfide bridges. One does not say that the "sequence" of a peptide or protein has been altered merely because there is a disulfide bridge is present.

The next issue concerns that of "damage" due to ROS, versus the teachings of the reference with regard to efficacy. The reference discloses that the peptides are effective to reduce tumor cell volumes by inhibiting angiogensis. However, the oncologist of ordinary skill would reason that tumor cells give rise to ROS, and so if fewer tumor cells are present, a smaller quantity of ROS will be produced. If a smaller quantity of ROS is produced, it stands to reason that the "damage" caused by those ROS's will also decline.

Thus, the claims are rendered obvious.

✧

Claims 1, 8-11, 21-26, 28-31 are rejected under 35 U.S.C. §103 as being unpatentable over Konishi (USP 4,461,724) in view of Ben-Hamida (*Inflammation research : Official Journal of the European Histamine Research Society* **47** (4) 193-9, 1998) or Danielsson D (*Digestive diseases and Sciences* **43** (9 Suppl) 167S-173S, 1998) or Iinuma S (*Digestive Diseases and Sciences* **43** (8) 1657-64, 1998) or Manjari V (*Prostaglandins, leukotrienes, and Essential Fatty Acids* **59** (6) 401-6, 1998) or Norgaard (*Journal of infectious diseases* **174** (3) 544-51, 1996).

As indicated previously, Konishi discloses the use of peptides for treating ulcers. The peptides contain a histidine residue which is located 3 amino acids from the N-terminus, as required of the instant claims. Konishi does not disclose that the symptoms of ulcers are mediated by "ROS". Each of Ben-Hamida, Danielsson, Iinuma, Manjari, and Norgaard disclose that ulcers are mediated by "ROS".

As indicated, Konishi does not teach that the anti-ulcer effect derives directly from inhibiting the production of ROS. However, each of the secondary references discloses that the presence of *Helicobacter* gives rise (directly or indirectly) to production of ROS. Thus, perhaps the peptides of Konishi are acting by sequestering metal ions, leading to decreased ROS production. Or perhaps the peptides of Konishi inhibit one of the cellular processes of *Helicobacter*, leading to decreased proliferation of the bacteria which in turn leads to decreased production of ROS. Or perhaps the peptides act by inhibiting neutrophil oxidase. Or perhaps the peptides do not actually inhibit the production of ROS, but instead accelerate healing of the affected tissues. Regardless of which of these mechanisms may be acting, the result is that the "damage" caused by the ROS will be mitigated if the peptides are in fact effective to successfully treat patients afflicted with ulcers.

Thus, the claims are rendered obvious.

✧

Claims 1, 4, 9-11, 21-24, 28-30 are rejected under 35 U.S.C. §103 as being unpatentable over Hahn (USP 4,816,449) in view of Gaffar (USP 4,975,423).

Hahn discloses (col 15, table 2) that the following peptide inhibits NK cell-induced cytotoxicity: Ala-Arg-His-Ser

Hahn does not disclose that NK cells produce ROS.

Gaffar discloses (col 1, line 30+) that NK cells cause "damage" by producing reactive oxygen species. Gaffar does not disclose any peptide falling within the scope of claim 1.

Thus, it would have been obvious to one of ordinary skill that by contacting the tetrapeptide A-R-H-S with NK cells, the amount of ROS produced will be reduced, and hence the "damage" caused by the ROS will be reduced also.

✧

Claims 1, 4, 9-11, 21-24, 28-30 are rejected under 35 U.S.C. §103 as being unpatentable over Hahn (USP USP 4628045) in view of Gaffar (USP 4,975,423).

Hahn discloses (table 5, col 23) that the following peptide inhibits NK cell induced cytotoxicity: Ala-Arg-His-Ser

Hahn does not disclose that NK cells produce ROS.

Gaffar discloses (col 1, line 30+) that NK cells cause "damage" by producing reactive oxygen species. Gaffar does not disclose any peptide falling within the

scope of claim 1.

Thus, it would have been obvious to one of ordinary skill that by contacting the tetrapeptide A-R-H-S with NK cells, the amount of ROS produced will be reduced, and hence the "damage" caused by the ROS will be reduced also.

✧

Claims 1, 4, 9, 10, 21-24, 28-30, 375-381 are rejected under 35 U.S.C. §103 as being unpatentable over Heavner (WO 94/14836).

Heavner discloses (p. 26, line 21 and page 46, line 19) various peptides for treating ischemia. Among them is SEQ ID NO: 21, which is the following: SK**H**KLALCY (see, e.g., page 10, line 32; page 24, line 25).

The artisan of ordinary skill would reason that if a compound is effective to treat ischemia, then the compound is also effective to reduce the "damage" that results in the manifestations of symptoms of the ischemia.

Thus, the claims are rendered obvious.

✧

Claims 1, 4, 9, 10, 21-24, 28-30, 375-381 are rejected under 35 U.S.C. §103 as being unpatentable over Heavner (WO 94/14836) in view of Moyle (USP 5,919,900) or Nierman (USP 5,529,907) or Serhan (USP 6,008,205).

Heavner discloses (p. 26, line 21 and page 46, line 19) various peptides for treating

ischemia. Among them is SEQ ID NO: 21, which is the following: SK**H**KLALCY (see, e.g., page 10, line 32; page 24, line 25). It is also disclosed that the peptides inhibit binding of neutrophils to P-selectin. In the "backround" section of Heavner, it is disclosed that compounds acting by the same mechanism as the disclosed peptides inhibit the binding of neutrophils to endothelium. Heavner does not disclose that neutrophils produce ROS. Each of Moyle, Nierman and Serhan disclose that neutrophils produce ROS. (See, e.g., col 1, line 34+ Serhan; col 2, line 65+ of Nierman; and several locations of Moyle such as col 1, line 45+ and col 2, line 60).

One of ordinary skill in possession of the references would determine that the peptides of Heavner will reduce the recruitment of neutrophils to the site of injury, and hence the "damage" caused by the neutrophils at that site will be reduced.

Thus, the claims are rendered obvious.

✧

Claims 1, 9, 21-24, 28-30, 375-381 are rejected under 35 U.S.C. §103 as being unpatentable over Saitoh (WO 94/09808).

Saitoh discloses various peptides for treating neurological disease, or ischemia (e.g., col 6, line 21). Among the peptides asserted to be effective in this regard is the peptide designated SEQ ID NO: 8 (see page 18 and page 40). The sequence of this peptide is the following: AK**H**RERMSQVM

The artisan of ordinary skill would reason that if a compound is effective to treat ischemia, then the compound is also effective to reduce the "damage" that results in the manifestations of symptoms of the ischemia.

Thus, the claims are rendered obvious.

✧

Claims 1, 9, 21-24, 28-30, 375-381 are rejected under 35 U.S.C. §103 as being unpatentable over Saitoh (WO 94/09808) in view of Hensley (*Ann N. Y. Acad. Sci.* 786:120-134, 1996)

Saitoh discloses various peptides for treating neurological disease such as Alzheimer's. Among the peptides asserted to be effective in this regard is the peptide designated SEQ ID NO: 8 (see page 18 and page 40). The sequence of this peptide is the following:

AK**H**RERMSQVM

Saitoh does not disclose that Alzheimer's Disease is mediated by ROS. However, Hensley discloses that Alzheimer's Disease is mediated by ROS.

Thus, the artisan of ordinary skill would reason that if a compound is effective to treat Alzheimer's Disease, then the compound is also effective to reduce the "damage" that is caused in patients afflicted with the disorder.

Thus, the claims are rendered obvious.

✧

Claims 1, 9-11, 21-24, 28-30, 375-381 are rejected under 35 U.S.C. §103 as being unpatentable over Chen, Hua-Ming (*Food Factors for Cancer Prevention, [International Conference on Food Factors: Chemistry and Cancer Prevention]*, Hamamatsu, Japan, Dec., 1995 (1997), Meeting Date 1995, 639-641. Editor(s): Ohigashi, Hajime; Publisher: Springer, Tokyo, Japan) or Chen, Hua-Ming (*Journal of Agricultural and Food Chemistry* **46**(1), 49-53, 1998).

Chen (1998) discloses (table 1 page 51) that various histidine-containing tripeptides and tetrapeptides inhibit the production of ROS. This is also disclosed on page 640 of Chen (1997). Accordingly, a chemist of ordinary skill would reason that if the production of ROS can be inhibited, the "damage" caused by ROS will be reduced.

Thus, the claims are rendered obvious.

✧

Claims 1, 9, 10, 21-24, 28-30, 375-381 are rejected under 35 U.S.C. §103 as being unpatentable over Morikawa, Eiharu (*Stroke* (Dallas) **27**(5), 951-956, 1996) or Seko, Yoshinori (*Journal of Pathology* **178**(3), 335-42, 1996).

Morikawa discloses the following peptide (p. 952, col 1, line 2): YTHLVAIQ This peptide is also disclosed in Seko (page 336, col 1, line 6). Both references disclose that the peptide is effective to treat ischemia. One of ordinary skill would have

reasoned that if a peptide is effective to treat ischemia, the "damaging" effects that gave rise to the symptoms of ischemia would be reduced.

✧

Claims 1, 9, 10, 21-24, 28-30, 375-381 are rejected under 35 U.S.C. §103 as being unpatentable over Kaplan (*Neuroscience Research Communications* **19**(2), 115-123, 1996)

Kaplan discloses that the following peptide is effective to treat one or more symptoms of ischemia: MEHFPGP

The artisan of ordinary skill would reason that if a compound is effective to treat ischemia, then the compound is also effective to reduce the "damage" that results in the manifestations of symptoms of the ischemia.

Thus, the claims are rendered obvious.

*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at 571-272-0951. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

D. Lukton

DAVID LUKTON
PATENT EXAMINER
GROUP 1600